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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/603,800 | 06/26/2003 | Junji Hamuro | 238027US0CONT | 7806 |

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| EXAMINER | |
|---|---|
| NGUYEN, QUANG | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1633 | |

DATE MAILED: 10/05/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/603,800 | HAMURO ET AL. | |
| | Examiner | Art Unit | |
| | Quang Nguyen, Ph.D. | 1633 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *14 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *21-39* is/are pending in the application.

4a) Of the above claim(s) *24 and 25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-23 and 26-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.



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## DETAILED ACTION

Applicant's amendment filed on 7/14/05 has been entered.

New claims 21-39 are pending in the present application.

Applicants elected previously with traverse the following species: (a) macrophages as a cell species; (b) N,N'-diacylcystine as a species of a substance; and (c) corneal epithelium as a species of an organ, in the reply filed on 12/23/04.

Claims 24-25 are withdrawn from further consideration because they are directed to non-elected species.

Accordingly, new claims 21-23 and 26-39 are examined on the merits herein with the above elected species.

### *Response to Amendment*

The rejection under 35 U.S.C. 102(b) as being anticipated by Hamuro et al. (EP 1 004 302 A2, IDS) is withdrawn in light of Applicant's amendment.

### *Claim Objections*

Claims 24-25 are objected to because the phrase "the substance" is duplicated in the claims. Appropriate correction is required.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21-23 and 26-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method of suppressing a rejection to a minor antigen in an allograft, said method comprises administering to a recipient of said allograft an effective amount a composition comprising a substance having a function of decreasing a reduced glutathione content in at least one cell selected from the group consisting of macrophages, monocytes and dendritic cells, and thereby the rejection to a minor antigen in said allograft is suppressed;

does not reasonably provide enablement for a method of suppressing any other organ transplant rejections. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. ***This is a new ground of rejection.***

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

The instant specification is not enabled for the broadly claimed invention for the reasons discussed below.

***1. The breadth of the claims***

The claims are drawn to a method of **suppressing any rejection of any organ transplant in a recipient** by administering to an organ transplant recipient an effective amount of a composition comprising **any substance** having a function of decreasing a reduced glutathione content in at least one cell selected from the group consisting of macrophages, monocytes and dendritic cells, with macrophages as a cell species; N,N'-diacylcystine as a species of a substance; and corneal epithelium as a species of an organ .

***2. The state and the unpredictability of the prior art***

At the effective filing date of the present application (12/26/03), little was known on the use of any substance, particularly N,N'-diacylcystine, having a function of decreasing a reduced glutathione content in at least one cell selected from the group consisting of macrophages, monocytes and dendritic cells to suppress any organ transplant rejections in an organ transplant recipient. In addition, the physiological art is recognized to be unpredictable.

***3. The amount of direction or guidance provided***

The instant specification fails to provide sufficient guidance, and particularly any relevant example demonstrating that the administration of a composition comprising any substance having a function of decreasing a reduced glutathione content in at least one cell selected from the group consisting of macrophages, monocytes and dendritic cells is sufficient to suppress any organ transplant rejection, including a xenogeneic organ transplant, in a recipient. On the contrary, several years after the effective filing date of

the present application Applicants clearly demonstrated that N,N'-diacetyl-L-cystine dimethylester and diethyl maleate are capable of modulating the intracellular thiol rdox status **that has suppressive effects on the rejection of minor H incompatible-, but not of MHC-incompatible grafts** (see the entire article, particularly page 450, right hand column, last paragraph continues to first paragraph of left hand column on page 451); let alone for any other organ transplant rejections as broadly encompassed by the instant claims. The instant specification fails to provide any specific guidance or parameters or conditions under which other organ transplant rejections would be suppressed by the compositions of the presently claimed inventions. Since the prior art at the effective filing date of the present application fails to provide such guidance, it is incumbent upon the present application to do so. Otherwise, with the lack of sufficient guidance provided by the instant disclosure, it would have required undue experimentation for a skilled artisan to make and use the methods as claimed.

Accordingly, due to the lack of guidance provided by the specification regarding to the issues set forth above, the breadth of the claims, and the state of the relevant art, it would have required undue experimentation for one skilled in the art to make and **use** the instant broadly claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21-23 and 26-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. ***This is a new ground of rejection.***

In claim 21 and its dependent claims, there is no nexus between the reciting step of administering to an organ transplant recipient an effective amount of a composition comprising a substance having a function of decreasing a reduced glutathione content in at least one cell selected from the recited Markush group with the preamble of the claims that recites "a method of suppressing a rejection of an organ transplant rejection". Clarification is requested because the metes and bounds of the claims are not clearly determined.

***It is noted that this Office Action contains rejections of the same claims under 35 USC 112, 1st paragraph and 35 USC 102(b) below. While these rejections may seem contradictory, they are not because each is based upon a different legal analysis, e.g., sufficiency of the disclosure of the instant application to support claims under 35 USC 112, 1st paragraph vs sufficiency of a prior art disclosure to anticipate or render obvious an embodiment(s) of the claimed invention (See in re Hafner, 161 USPQ 783 (CCPA 1969)). Specifically, the instant specification fails to disclose or teach the specific conditioning method of Tomita et al. below.***

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 21-23, 26, 28-29, 32-34, 36-39 are rejected under 35 U.S.C. 102(b) as being anticipated by Tomita et al. (The Journal of Immunology 164:34-41, 2000; IDS). ***This is a new ground of rejection.***

Tomita et al disclose a method of drug (cyclophosphamide plus busulfan)-induced skin allograft tolerance in mice that can regularly overcome fully H-2-mismatched barriers in mice. The method comprises the steps of intravenous administration of 1 X $10^8$ allogeneic spleen cells on day 0, intraperitoneal injection of 200 mg/kg cyclophosphamide and 25 mg/kg busulfan on day 2, and intravenous injection of T-cell-depleted 1 x $10^7$ bone marrow cells from the same donor on day 3, and recipient mice prepared with this conditioning developed donor-specific tolerance and long-lasting survival of skin allografts (see abstract). Tomita et al further disclose that busulfan was dissolved in a minimal amount of DMSO followed by PBS at a concentration of 2 mg/kg, and on day 3 busulfan solution in a dose of 12.5-50 mg/kg was injected intraperitoneal (page 35, left hand column, fifth paragraph).

Since the claims encompass the method of Tomita et al that has the same method step and the same starting materials including a substance having a function of decreasing a reduced glutathione content in at least one cell selected from the group

consisting of macrophages, monocytes and dendritic cells (busulfan); the reference anticipates the instant claims.

## *Conclusion*

***No claims are allowed.***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, David Guzo, Ph.D., may be reached at (571) 272-0767, or SPE, Dave Nguyen, at (571) 272-0731.

**To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.**

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

QUANG NGUYEN, PH.D
PATENT EXAMINER